REMARKS

Examination of Claims 11, 13-20, 22, 24, 26, 28, and 33-42 is presented in the present Office action. Claims 11, 13, 33, 36-38, and 40 were objected to because of informalities in the claims. Claims 14, 15, 17, 20, 41, and 42 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Each of the rejections is addressed as follows.

Support for amendments

In claim 11, support for amending F^2 to include "nitrate group" can be found on page 4, line 28, of the application as filed, where F^2 is defined as a nitrate group in a preferred embodiment. In addition, the phrase "but is not a nitrate group," as it refers to G^2, has been removed because this text is redundant, with the subsequent limitation of G^2 to R^N-Z^N. Claim 14 has also been amended accordingly by deleting "not a nitrate group," as it refers to G^2.

Claims 11, 13, 17, 24, 26, 28, 33-41, have been amended to correct claim element antecedents, include/correct punctuation marks and/or conjunctions, correct plurality of claim elements, and remove redundant claim elements, such that the respective claim elements clearly set forth the metes and bounds of the patent protection desired.

In claim 11, the text, "a substituted or unsubstituted" has been inserted before "heterocyclic group." Support for this can be found in a number of claimed compounds of the invention, such as compounds IIIe, IIIf, IIIad, IIIah, IIIak, IIIai, IVk, Vr, Vt, and Vy.

In claim 14, the definitions for E, F^1, G^1, and G^2 have been removed to make this claim consistent with claim 11, from which it depends. The claim resulting from this amendment finds support in the application as filed on page 4, lines 4-8.

In claim 15, the claim has been simplified to more clearly reflect the limitation of "G^1 is a methylene group." Support for this claim can be found in claim 15 as originally

filed.

In claim 20, "SR^7", as it refers to Y, has been changed to "SSR^7," support for which can be found on page 6, line 21, and in claim 13 of the original application as filed.

In claim 41, the dependency has been changed so that this claim is now dependent on claim 11. Support for this can be found in the application as filed from page 3, line 10, to page 4, line 8, and in particular, on page 4, lines 4 through 8.

New claim 43 finds support in the application as filed on page 10, line 20.

Objection due to informalities

As suggested by Examiner, the body of claims 11, 13, 33, 36-38, and 40 has been tied to the preamble by changing the antecedent of the word "subject" when it appears for a second time in the claim from "a" to "said."

Rejection under 35 U.S.C. § 112, second paragraph

Examiner states that there is insufficient antecedent basis for the limitation "wherein F^2 is a nitrate group" in claims 14 and 15. Claim 11, from which these two claims depend, has been amended accordingly such that the definition of F^2 includes a nitrate group. In addition, in claim 14 the definitions for E, F^1, G^1, and G^2 have been removed in accordance with that found in claim 11, from which it depends.

Examiner states that there is insufficient antecedent basis in claim 17 for the limitation "R^2 and R^4 are the same or different and selected from … acyl groups ($-C(O)R^5$)." Applicants respectfully direct Examiner's attention to claim 13, from which claim 17 ultimately depends, where either R^2 or R^4 can be A, which can in turn be an "aliphatic moiety having from 1-24 carbons in the chain, containing linkages selected from the groups consisting of C=O …. , which optionally may contain O …. in the chain," thereby encompassing an acyl group defined by $-C(O)R^5$.

Examiner states that there is insufficient antecedent basis for the limitations

"PO_3HM" and "SR^7" in claim 20. In the latter case, Applicants thank examiner for noting this typographical error and have amended the claim appropriately, changing "SR^7" to "SSR^7." As for the lack of antecedent basis for "PO_3HM", Applicants respectfully point out that in claim 13, from which claim 20 ultimately depends, PO_3HM is present when Y is $P(O)(OR^{16})(OM)$ and R^{16} is H. In addition, Examiner states that claim 20 is vague and indefinite due to the limitation "or C_1 or C_2 connections to R^1 or R^3 in cyclic derivatives." Applicants respectfully disagree and argue that one skilled in the art would understand that a C_1 or C_2 connection from any of the cited radicals (R^5, R^6, R^8, R^9, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}) to R^1 or R^3 in cyclic derivatives means that a ring is formed which includes one of the cited radicals, R^1 or R^3, and one or two carbons linking the radical to R^1 or R^3, the size of the ring formed being determined by the radical and the moiety that contains it, R^1 or R^3 and the moiety that contains it, and the linking carbons.

To further establish how connections to form ring systems would be viewed by one skilled in the art, a signed declaration of Dr. Gregory Thatcher under 37 C.F.R. § 1.132 is attached. In addition, this claim has been amended to better reflect the metes and bounds of this claim by making the language clearer.

Examiner states that the limitations set forth in claims 41 and 42 have no antecedent basis. Applicants direct Examiner's attention to the change of dependency of claim 41 from claim 13 to claim 11, thereby reestablishing an antecedent basis. Applicants also note that claim 42 has been cancelled.

CONCLUSION

Applicants submit that the claims, as amended, are in condition for allowance, and such action is requested. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Applicants respectfully request that, effective immediately, all communication in this case be addressed to:

Kristina Bieker-Brady, Ph.D.
Clark & Elbing LLP
101 Federal Street
Boston, MA 02110

Respectfully submitted,

Date: September 5, 2003

Kristina Bieker-Brady, Ph.D.
Reg. No. 39,109

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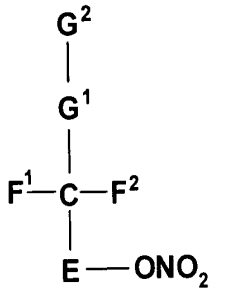
Claims 1 – 10 (Cancelled)

11. (Currently amended) A method for providing sedation, mitigating anxiety or providing anaesthesia in a subject in need thereof, comprising administering to the subject an effective amount of a therapeutic compound, wherein said therapeutic compound is of the formula (Ia):

(Ia) 

, in which

F^2 is a nitrate group or an organic radical which may be joined in a cyclic ring system with G^2, and which may contain inorganic counterions;

E is a methylene group;

G^1 is a methylene group or does not exist;

F^1 is H; and

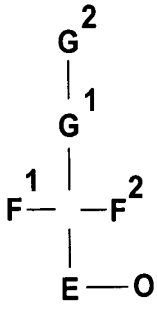
G^2 is R^N-Z^N; wherein R^N is an organic radical possessing a heteroaryl group containing a P or S atom, where said P or S is positioned β, γ, or δ to a nitrate group; and Z^N is W^N_{mm}-X^N_{nn}-Y^N_{oo}; wherein

mm, nn, oo are 0 or 1 and W^N, X^N, Y^N are NH, NR^{NN}, CO, O, or CH_2; wherein

R^{NN} is a $C_1 - C_{12}$ alkyl group.

12. (Cancelled)

13 (Currently amended) A method for providing sedation, mitigating anxiety or providing anaesthesia in a subject in need thereof, comprising administering to said subject an effective amount of a therapeutic compound, wherein said therapeutic compound is of the formula (Ic):



(Ic), in which

E is $(R^1R^2C)_m$ and $G^2–G^1–CF^1F^2–$ is $R^{19}–(R^3R^4C)_p–(R^{17}R^{18}C)_n–$; wherein each of m, n, and p is an integer from 0 to 10;

$R^{3,17}$ are each independently hydrogen, a nitrate group, or A; and

$R^{1,4}$ are each independently hydrogen, or A;

where A is selected from a substituted or unsubstituted aliphatic group comprising a branched or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in the chain, which optionally may contain O, S, NR^6, or an unsaturation in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino, aryl, or heterocyclic groups; an unsubstituted or substituted cyclic aliphatic moiety having from 3 to 7 carbon atoms in the aliphatic ring, which optionally may contain O, S, NR^6, or an unsaturation in the ring, optionally bearing from 1 to 4 hydroxy, nitrate, amino, aryl, or heterocyclic groups; an unsubstituted or substituted aliphatic moiety constituting a linkage of from 0 to 5 carbons, between R^1 and R^3 and/or between R^{17} and R^4, which optionally may contain O, S, NR^6, or an unsaturation in the linkage, and optionally bearing from 1 to 4 hydroxy, nitrate, amino, aryl, or heterocyclic groups; a substituted or unsubstituted aliphatic group comprising a branched, cyclic or straight-chain aliphatic moiety having from 1 to 24 carbon atoms in

the chain, containing linkages selected from the group consisting of C=O, C=S, and C=NOH, which optionally may contain O, S, NR^6, or an unsaturation in the chain, optionally bearing from 1 to 4 hydroxy, nitrate, amino, aryl, or heterocyclic groups; a substituted or unsubstituted aryl group; a substituted or unsubstituted heterocyclic group; an amino group selected from alkylamino, dialkylamino, cyclic amino, diamino, triamino, arylamino, diarylamino, and alkylarylamino moieties; hydroxy; alkoxy; and a substituted or unsubstituted aryloxy; wherein

X is F, Br, Cl, NO_2, CH_2, CF_2, O, NH, NMe, CN, NHOH, N_2H_3, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_2HM, PO_3HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, C(O), $C(O)R^{12}$, $C(O)(OR^{13})$, PO_2H, PO_2M, $P(O)(OR^{14})$, $P(O)(R^{13})$, SO, SO_2, $C(O)(SR^{13})$, SR^5, SSR^7 or SSR^5;

Y is F, Br, Cl, CH_3, CF_2H, CF_3, OH, NH_2, NHR^6, NR^6R^7, CN, NHOH, N_2H_3, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_2HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, $C(O)R^{12}$, $C(O)(OR^{13})$, $C(O)(SR^{13})$, SR^5, SSR^7 or SSR^5, or does not exist;

each of R^2, R^5, R^{18}, and R^{19} is, independently, hydrogen, A, or X-Y;

each of R^6, R^7, R^8, R^9, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} is, independently, an alkyl or acyl group containing 1-24 carbon atoms, which may contain 1-4 ONO_2 substituents; a C_1 - C_6 connection to R^1 – R^4 in a cyclic derivative, which may contain 1-4 ONO_2 substituents; a hydrogen, a nitrate group, or A;

M is H, Na^+, K^+, NH_4^+, or $N^+H_kR^{11}{}_{(4-k)}$, where k is 0-3; or other pharmaceutically acceptable counterion;

and with the proviso that when m = n = p = 1 and R^{19}, R^2, R^{18}, R^1 = H and R^{17}, R^3 are nitrate groups, R^4 is not H.

14. (Currently amended) The method of claim 11, wherein F^2 is a nitrate group; with the proviso that when E and G^1 are methylene groups and F^1 is H, G^2 is not R^N-Z^N; wherein

R^N is any aryl or heteroaryl group and Z^N is $(CO)_{mm}$-X^N_{nn}-Y^N_{oo}; wherein

mm, nn, oo are 0 or 1 and X^N,Y^N are NH, NR^{NN}, O or CH_2; wherein

R^{NN} is a $C_1 - C_{12}$ alkyl group.

15. (Previously presented) The method of claim 11, wherein F^2 is a nitrate group; E and G^1 are methylene groups; F^1 is H; and G^2 is R^N-Z^N; wherein

R^N is an organic radical possessing an heteroaryl group containing P or S atoms where said P or S are positioned β, γ, or δ to a nitrate group as identified in formula Ia; and Z^N is W^N_{mm}-X^N_{nn}-Y^N_{oo}; wherein

mm, nn, oo are 0 or 1 and W^N, X^N, Y^N are NH, NR^{NN}, CO, O or CH_2; wherein

R^{NN} is a $C_1 - C_{12}$ alkyl group.

16. (Original) The method of claim 13, wherein R^{19} is X-Y.

17. (Currently amended) The method of claim 16, wherein:

R^1 and R^3 are the same or different and selected from H and C_1-C_4, alkyl chains, which chains may include one O linking R^1 and R^3 to form pentosyl, hexosyl, cyclopentyl, or cyclohexyl rings, which rings may optionally bear hydroxyl substituents;

R^2 and R^4 are the same or different and selected from H, a nitrate group, a C_1-C_4 alkyl chain, optionally bearing 1-3 nitrate groups, and an acyl group (-$C(O)R^5$);

R^7 and R^{11} are the same or different $C_1 - C_8$ alkyl or $C_1 - C_8$ acyl;

each of R^5, R^6, R^8, R^9, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} is, independently, an alkyl group containing 1-12 carbon atoms, which may contain 1-4 ONO_2 substituents; or a C_1 or C_2

connection to R^1 - R^3 in a cyclic derivative; and

M is H, Na^+, K^+, NH_4^+ or $N^+H_kR^{11}_{(4-k)}$, where k is 0-3.

18. (Original) The method of claim 17, wherein m = 1, n = 0, p=1.

19. (Previously presented) The method of claim 18, wherein:

X is CH_2, O, NH, NMe, CN, NHOH, N_2H_3, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, S, SCN, $SCN_2H_2(R^{15})_2$, $SCN_2H_3(R^{15})$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_3HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, C(O), $C(O)R^{12}$, $C(O)(OR^{13})$, PO_2M, $P(O)(OR^{14})$, $P(O)(R^{13})$, SO, SO_2, $C(O)(SR^{13})$, or SSR^5; and

Y is CN, $N_2H_2R^{13}$, $N_2HR^{13}R^{14}$, N_3, SCN, $SCN_2H_2(R^{15})_2$, $SC(O)N(R^{15})_2$, $SC(O)NHR^{15}$, SO_3M, SR^4, SO_2M, PO_3HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, $P(O)(OM)R^{15}$, CO_2M, CO_2H, CO_2R^{11}, $C(O)R^{12}$, $C(O)(SR^{13})$, SR^5, or SSR^5, or does not exist.

20. (Currently amended) The method of claim 18, wherein:

each of R^5, R^6, R^8, R^9, R^{12}, R^{13}, R^{14}, R^{15}, R^{16} is, independently, an alkyl group containing 1-12 carbon atoms, which may contain 1-4 ONO_2 substituents; or a C_1 or C_2 connection to R^1 - R^3 in a cyclic derivative

X is CH_2, O, NH, NMe, S, SO_3M, SH, SR^7, SO_2M, $S(O)R^8$, $S(O)_2R^9$, $S(O)OR^8$, $S(O)_2OR^9$, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, $P(O)(R^{15})(OR^8)$, PO_3HM or $P(O)(OM)R^{15}$; and

Y is SO_2M, SO_3M, PO_3HM, PO_3M_2, $P(O)(OR^{15})(OR^{16})$, $P(O)(OR^{16})(OM)$, SR^5, SSR^7 or SSR^5, or does not exist.

21. (Cancelled)

22. (Original) The method of claim 13, with the proviso that when m = n = p = 1 and R^{19}, R^2, R^{18}, R^1 = H and R^{17}, R^3 are nitrate groups, R^4 is not $C_1 - C_3$ alkyl.

23. (Cancelled)

24. (Previously presented) The method of any one of claims 11, 13, 14 or 15, further comprising administering said therapeutic compound with a pharmaceutically acceptable vehicle.

25. (Cancelled)

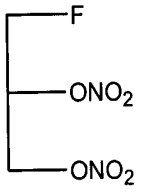
26. (Previously presented) The method of any one of claims 11, 13, 14, or 15, wherein said therapeutic compound modulates levels of the cyclic nucleotides cGMP and/or cAMP in said subject.

27. (Cancelled)

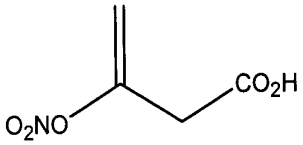
28. (Previously presented) The method of any one of claims 11, 13, 14, or 15, wherein said therapeutic compound modulates guanylyl cyclase activity in said subject.

Claims 29-32 (Cancelled)

33. (Currently amended) A method of providing sedation or mitigating anxiety in a subject in need thereof, comprising administering to the subject an effective amount of a therapeutic compound selected from the group consisting of:



IIIa,



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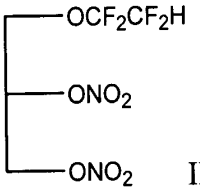

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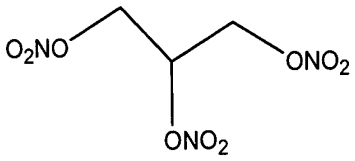

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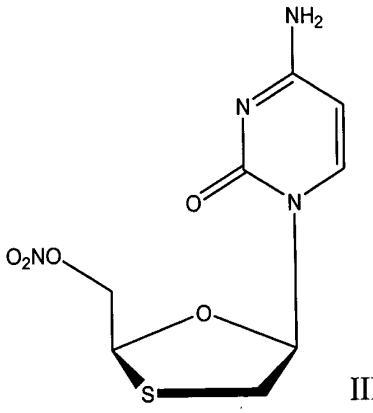

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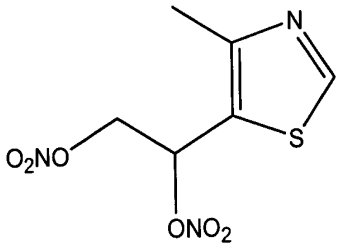

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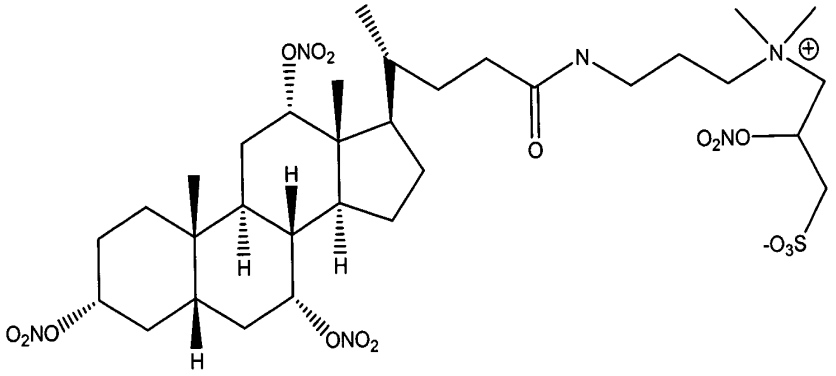

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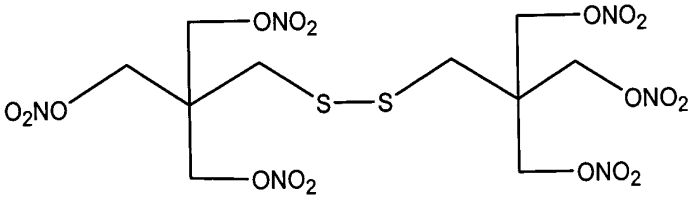

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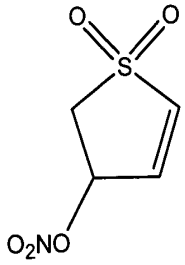

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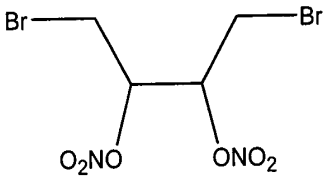

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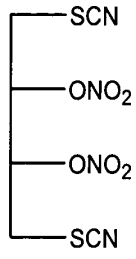

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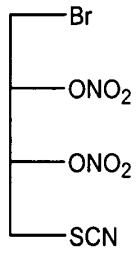

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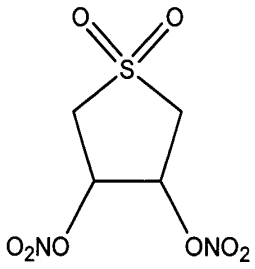

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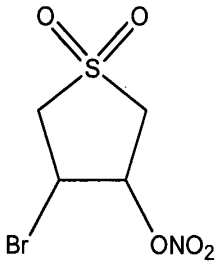

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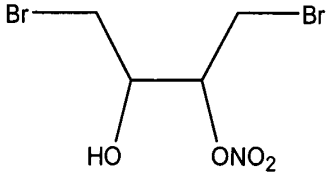

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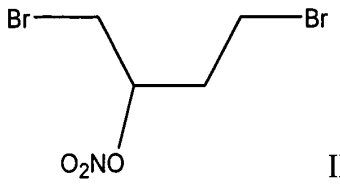

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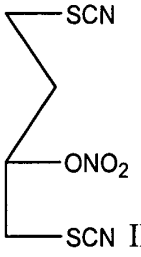

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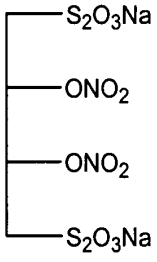

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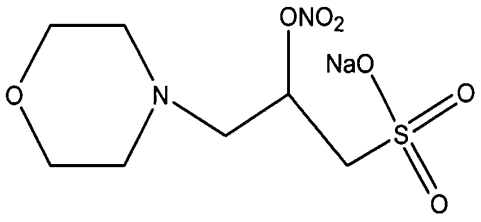
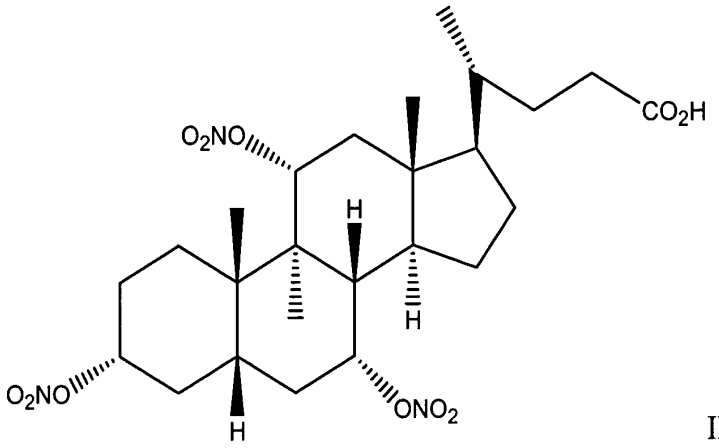
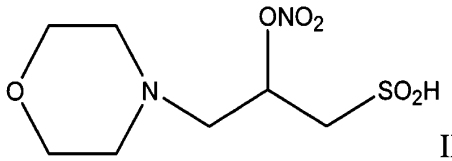


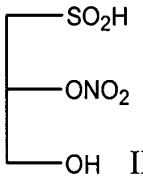
IIIs,



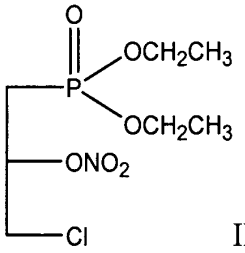
IIIt,



IIIu,



IIIv,



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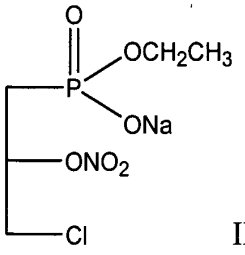

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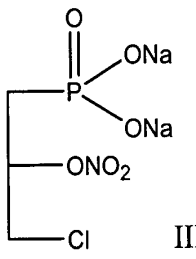
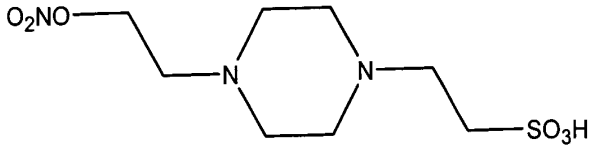


IIIy,



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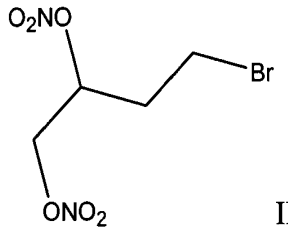
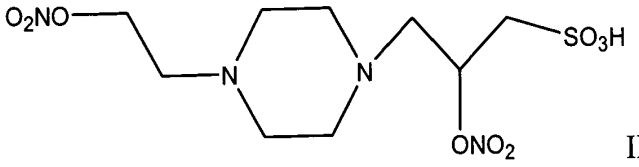


IIIaa,



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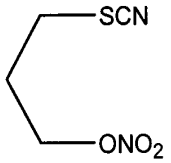

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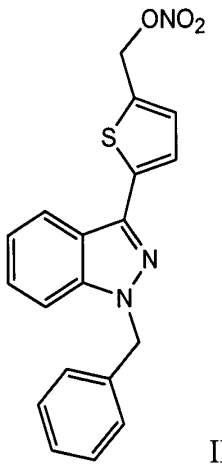

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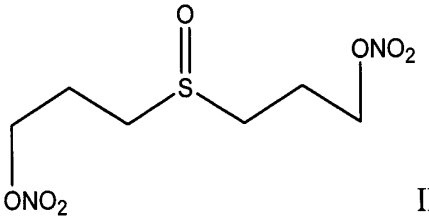
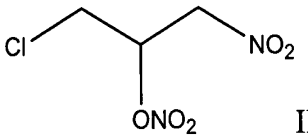


IIIae,



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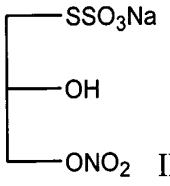
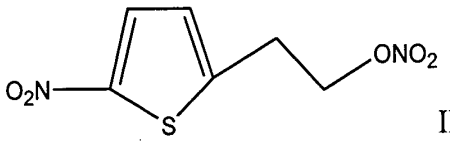
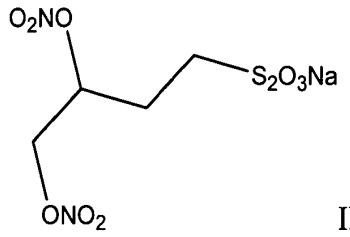


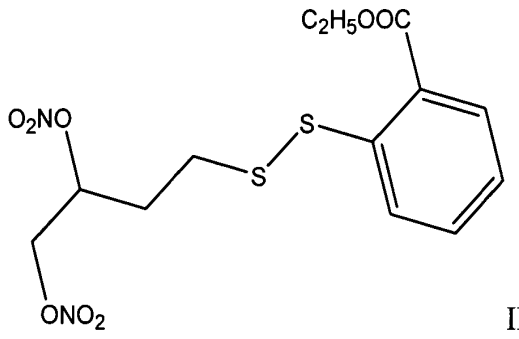
IIIag,



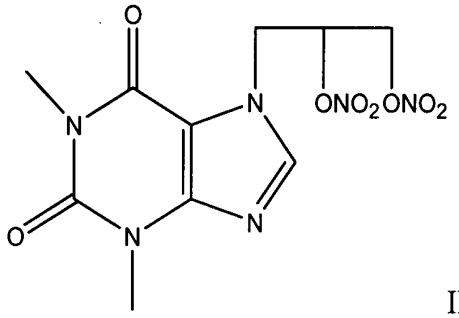
IIIah,



IIIai,



IIIaj,



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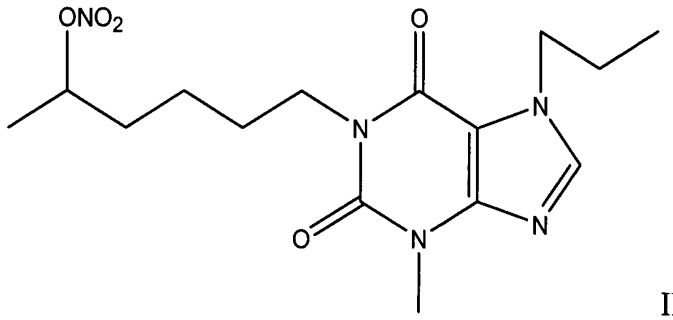
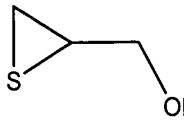
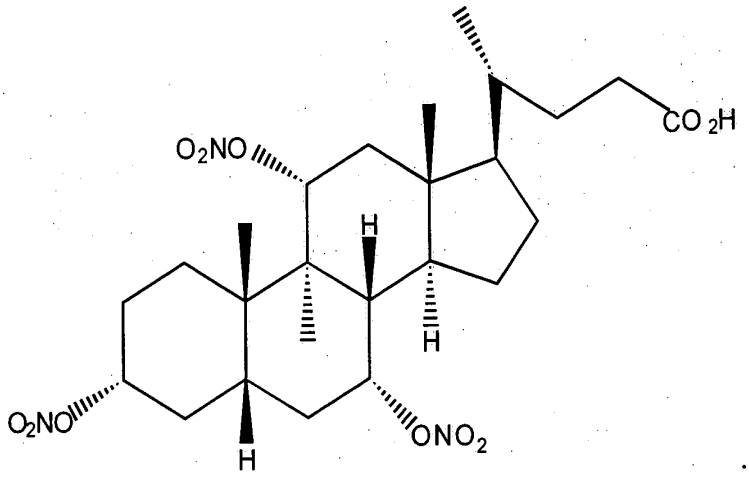


IIIal, and

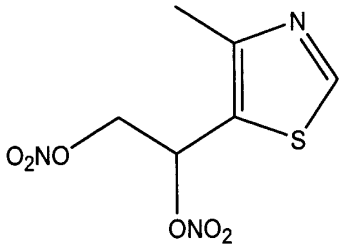


IIIam.

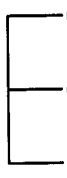
34. (Currently amended) The method of claim 33, wherein said compound has the formula IIIt:



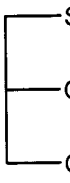
35. (Currently amended) The method of claim 33, wherein said compound has the formula IIIf:



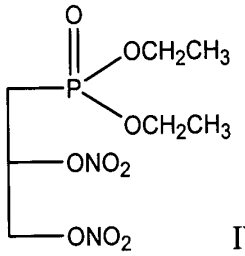
36. (Currently amended) A method of providing sedation or mitigating anxiety in a subject in need thereof, comprising administering to said subject an effective amount of a therapeutic compound selected from the group consisting of:



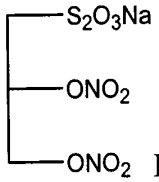
IVa,



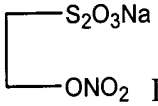
IVb,



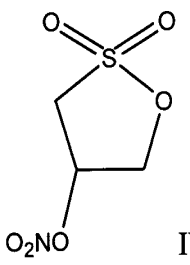
IVc,



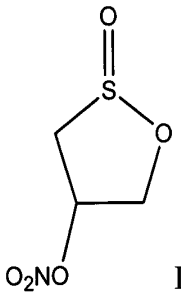
IVd,



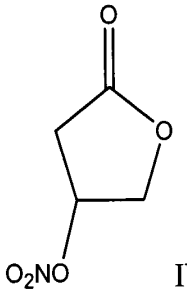
IVe,



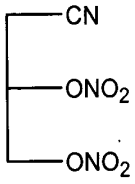
IVf,



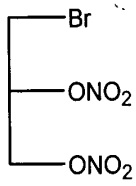
IVg,



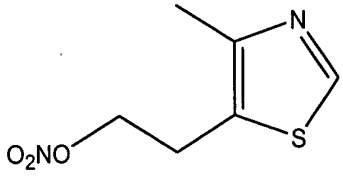
IVh,



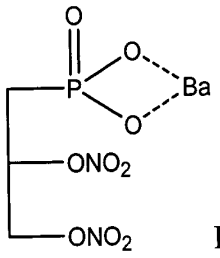
IVi,



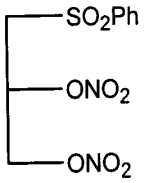
IVj,



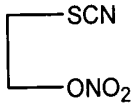
IVk,



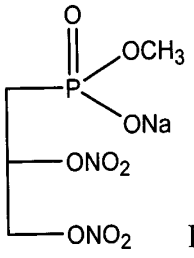
IVl,



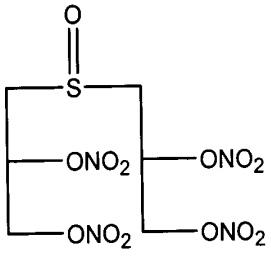
IVm,



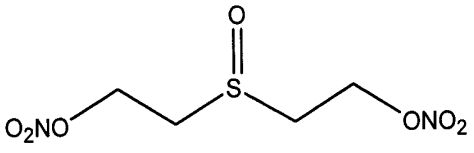
IVn,



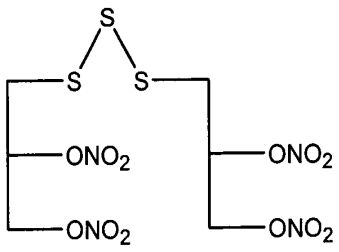
IVo,



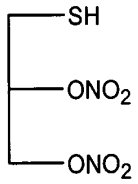
IVp,



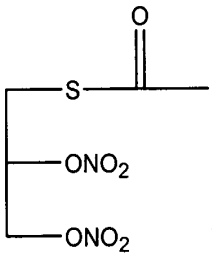
IVq,



IVr,

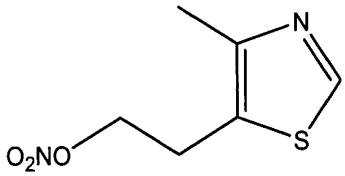


IVs, and



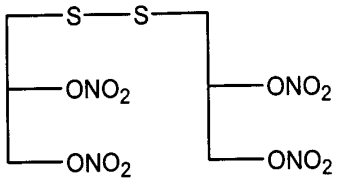
IVt.

37. (Currently amended) A method of providing sedation in a subject in need thereof, comprising administering to said subject an effective amount of a therapeutic compound having the formula IVk:

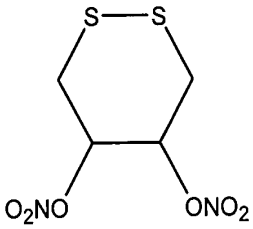


IVk.

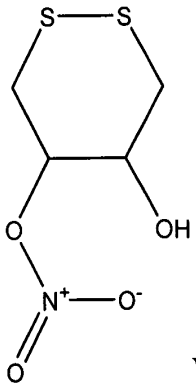
38. (Currently amended) A method of mitigating anxiety in a subject in need thereof, comprising administering to the subject an effective amount of a therapeutic compound selected from the group consisting of:



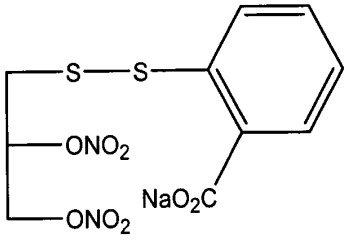
Va,



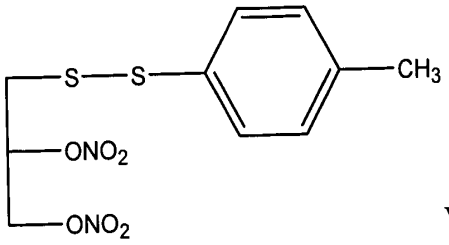
Vb,



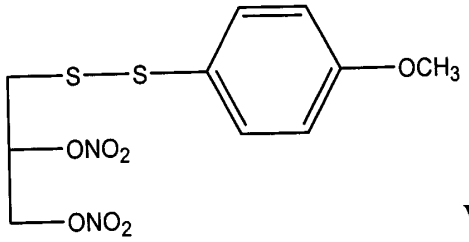
Vc,



Vd,


S
S
CH3
ONO2
ONO2

Ve,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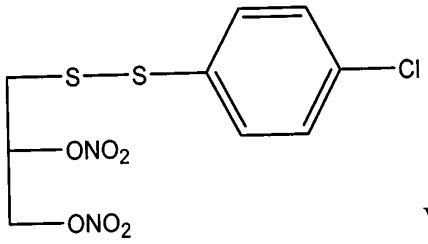
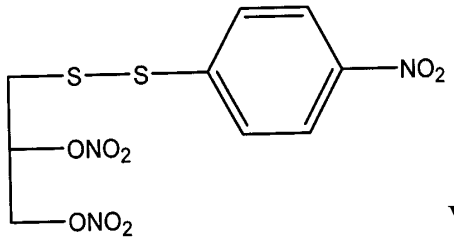
S
OCH3
ONO2
ONO2

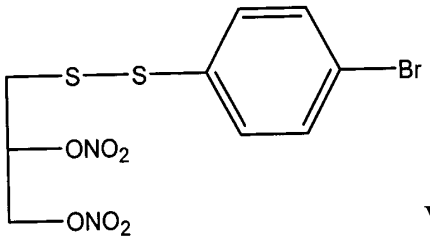
Vf,


S
S
Cl
ONO2
ONO2

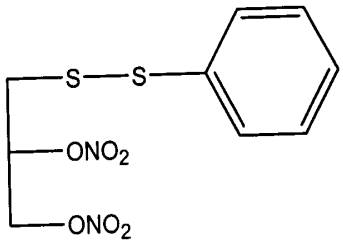
Vg,


S
S
NO2
ONO2
ONO2

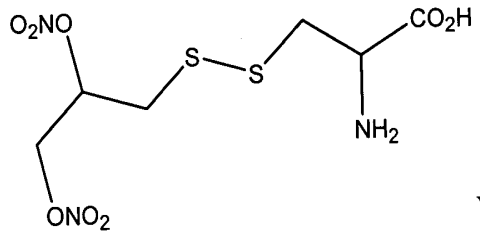
Vh,


S
S
Br
ONO2
ONO2

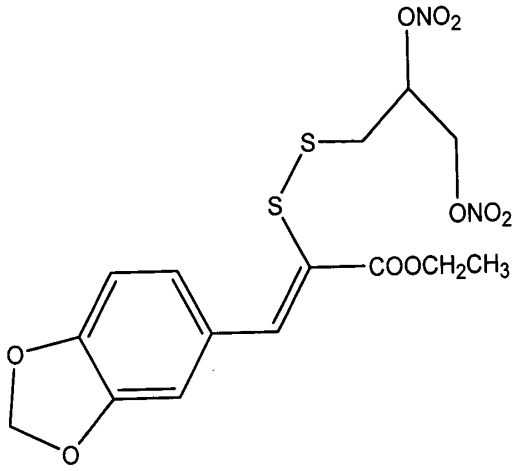
Vi,


S
S
ONO2
ONO2

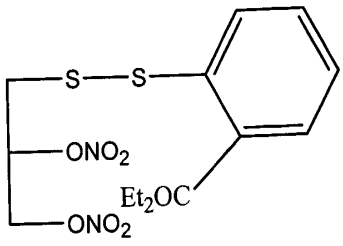
Vj,


O2NO
S
S
CO2H
NH2
ONO2

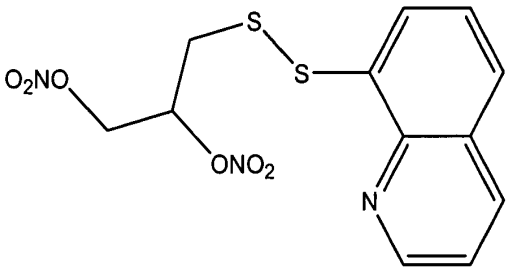
Vk,


ONO2
S
S
ONO2
COOCH2CH3
O
O

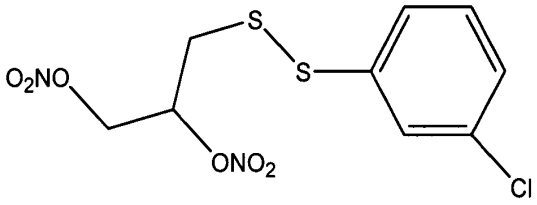
Vl,


S
S
ONO2
Et2OC
ONO2

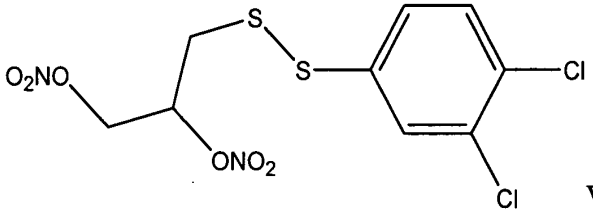
Vm,



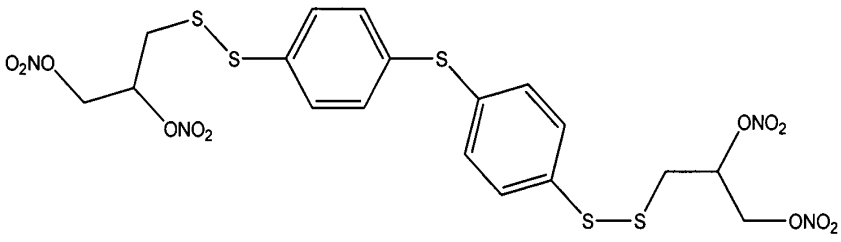
Vn,



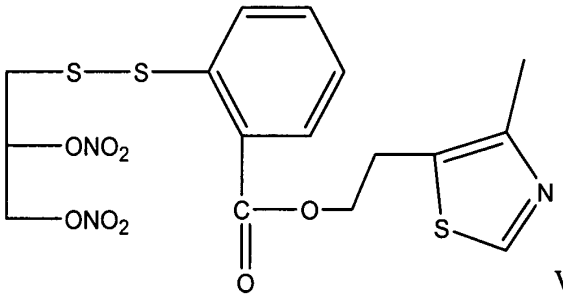
Vo,



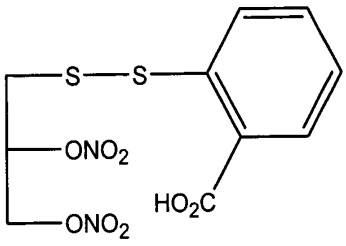
Vp,



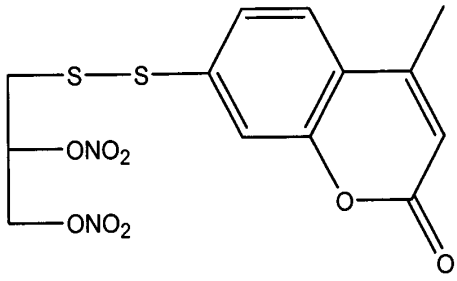
Vq,



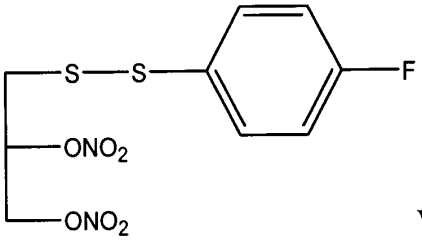
Vr,


S—S
ONO2
ONO2
HO2C

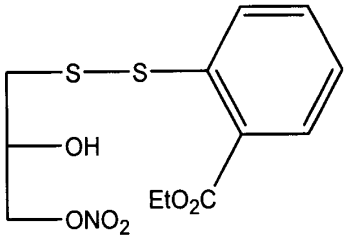
Vs,


S—S
ONO2
ONO2
O
O

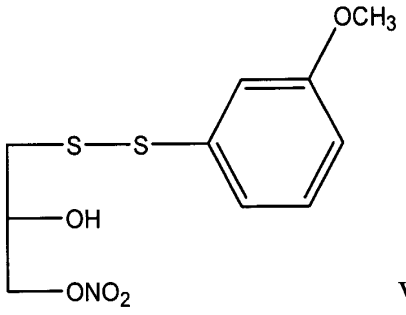
Vt,


S—S
F
ONO2
ONO2

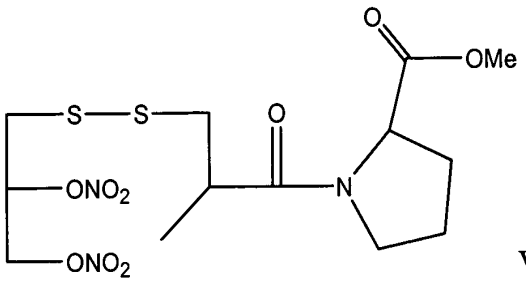
Vu,


S—S
OH
ONO2
EtO2C

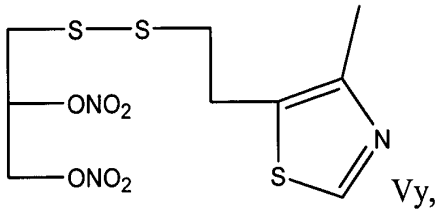
Vv,


OCH3
S—S
OH
ONO2

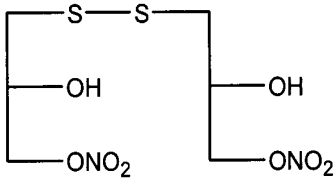
Vw,



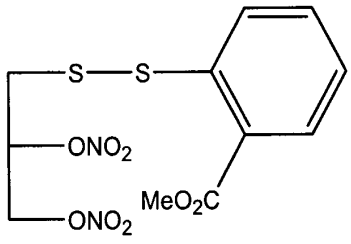
Vx,



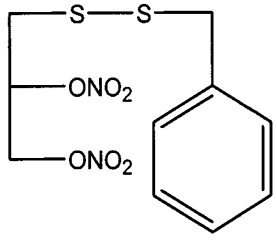
Vy,



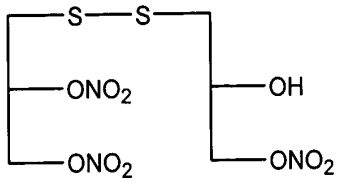
Vz,



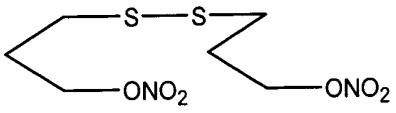
Vaa,



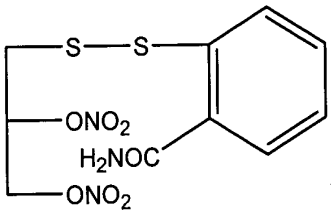
Vab,



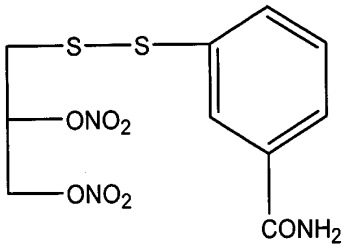
Vac,



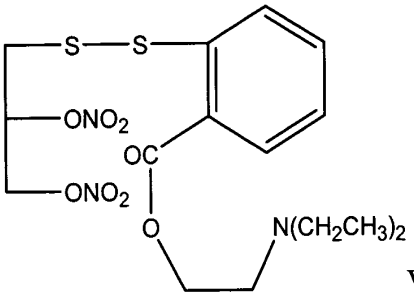
Vad,



Vae,

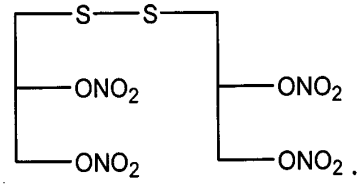


Vaf, and

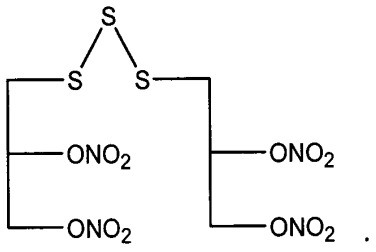


Vag.

39. (Currently amended) The method of claim 38, wherein said compound has the formula Va:



40. (Currently amended) A method of mitigating anxiety in a subject in need thereof, comprising administering to said subject an effective amount of a therapeutic compound having the formula IVr:



41. (Currently amended) The method of claim 11, wherein

G^2 is not R^N-Z^N; wherein

R^N is any aryl or heteroaryl group and Z^N is $(CO)_{mm}$-$X^N{}_{nn}$-$Y^N{}_{oo}$; wherein

mm, nn, oo are 0 or 1 and X^N,Y^N are NH, NR^{NN}, O or CH_2; wherein

R^{NN} is a $C_1 - C_{12}$ alkyl group.

42. (Cancelled)

43. (New) The method of claim 16, wherein X and/or Y contains a sulfur-containing functional group.